because the individual components of the subject compositions are so recognized neither teaches nor suggests to one of ordinary skill in the arts related to pharmaceutical compounding the superior results obtained by combining them as Applicants have done. Further, such recognition, in the absence of a teaching of record that provides both motivation and direction to prepare Applicants' compositions by selecting specific components from among the many substances so recognized, does not render Applicants' Claims unpatentable over Bechgaard *et al.*

It is stated in the Office Action under reply that Bechgaard *et al.* teach anti-epileptic or anti-spasmotic agents as being useful in their compositions. In point of fact, Bechgaard *et al.* utilize well over two columns to list the many different types of therapeutic agents that can be administered via their compositions. Such a general disclosure can hardly suggest to one of ordinary skill in the art that a particular composition will possess superior efficacy in the transnasal administration of a single group of therapeutic agents among the many varied types and examples listed by the citation. There is simply neither motivation nor enablement for one of ordinary skill in the art to make the specific selections necessary to achieve Applicants' results other than an impermissible hindsight construction based on Applicants' own teachings.

While it is admitted that Bechgaard *et al.* state that alcohol, glycol and glycol ethers are well known carriers for nasal administration of hypnotics, the formulations disclosed therein are based on a specific narrowly defined group of glycol ethers, i.e. n-glycofurols, that function as solvents for the disclosed polymers. Bechgaard *et al.* draw a distinction between those specific glycol ethers and "conventional" similar ingredients that do not impart the improved properties to their compositions. Further, there is neither teaching not suggestion in Bechgaard *et al.* that compositions not based on the use of n-glycofurols would possess special advantages in comparison to known compositions suitable for administration to the mucous membranes. The fact that the compositions taught by Bechgaard *et al.* require these specific glycol ethers in a non-aqueous vehicles clearly teaches away from the use of "conventional" similar ingredients, including those utilized in Applicants' aqueous compositions.

It is stated in the Office Action under reply that Bechgaard *et al.* teach compositions that comprise polyethylene glycols having a molecular weight between 200 and 750 and may contain one or more surfactants, such as bile salts, lecithin and the like. Applicants have conceded that such substances are recognized as being useful in the formulation of pharmaceutical formulations that can be administered by transnasal administration. However, the disclosure thereof by Bechgaard *et al.* is only in the context of non-aqueous compositions utilizing particular glycol ethers as the solvent. There is no teaching in Bechgaard *et al.*, or for that matter in the record as a whole, that would motivate one of ordinary skill in the art to make two major modifications of the compositions taught by Bechgaard *et al.*, i.e. remove the n-glycofurols, clearly stated as being the key ingredient, and include water in the formulations.

The compositions of the present invention are fundamentally different from those taught by Bechgaard *et al.* The present compositions are aqueous, i.e. containing about 10% by volume water. Water is a required ingredient, as are a specific group of glycols and an aliphatic alcohol in a specified ratio further in combination with a biological surfactant, i.e. a bile acid or a lecithin. Such compositions are neither taught nor suggested by the citation. In distinct contrast, Bechgaard *et al.* teaches compositions that are substantially non-aqueous. The compositions given in the examples are primarily polyethylene glycol and combinations thereof with the claimed n-glycofurols. The n-glycofurols, clearly key ingredients of the compositions taught by Bechgaard *et al.*, are relied upon to show advantage for the disclosed compositions over the art-recognized glycols discussed in column 3, lines 26-32. It is also evident that the n-glycofurols taught by Bechgaard *et al.* are chemically distinct from the group of aliphatic glycols of Applicants' compositions. It is respectfully submitted that, in the absence of a specific motivating teaching, such a specialized ingredient cannot be read into the compositions of the Claims under consideration for the purpose of holding them unpatentable over Bechgaard *et al.*

There are aqueous compositions given by Bechgaard *et al.* in the examples as controls, i.e. saline and the vehicle for the product Lokilan®. It is noted that, among the listed additional ingredients given in column 7, are both water-absorbing polymers and water. The compositions are thereafter stated by Bechgaard *et al.* as being preferably more than 50% polyethylene glycols, the primary example given for water-absorbing polymers. In the list of compositions tested for stability in Example 11 of the citation is one containing 1% water. It is also noted that the polymer components contain 0.05% water, however, that must be assumed to be bound within the polymer in some manner. The fact that the addition of water did not decrease the stability of the compositions is characterized by Bechgaard *et al.* as "amazing" although the compositions containing water are not as stable as many of the others tested.

It is readily apparent that Bechgaard *et al.* expected that water would adversely affect the stability of their compositions. It is respectfully submitted that one of ordinary skill in the art would regard the teaching of Bechgaard *et al.* as suggesting that the disclosed compositions should not contain water. The non-aqueous solvent system of Bechgaard *et al.* certainly does not suggest that aqueous compositions containing about 10% by volume of water would even be stable, much less advantageous, for the delivery of medicaments via intranasal administration. It is stated in the Office Action under reply that the skilled artisan would optimize the amounts of the carriers, "...such as water, alcohol and glycol, with the expectation to achieve the desired absorption of the drug"(emphasis added). Since the compositions taught by Bechgaard *et al.* are substantially water-free and it is stated therein that it is amazing that the presence of water does not have a negative effect on stability, "optimizing the amounts of the components of the carrier" according to the teachings of Bechgaard *et al.*, as applied to water, would be to substantially eliminate it. This clearly teaches away from the compositions of the Claims under examination.

It is also stated in the Office Action under reply that it would be obvious for the skilled person to add alcohols and surfactants (bile salts or lecithin) to the carrier taught by Bechgaard *et al.* It is conceded that the list of additional ingredients that may be

present in the Bechgaard *et al.* compositions includes alcohols and surfactants, but with no further distinction given for either term. It is respectfully submitted that there is neither teaching nor suggestion in Bechgaard *et al.* of the advantages of combining any members of the long list of possible additional ingredients in a transnasal composition. In fact, that sole ingredient that is stated as conveying the advantageous properties to the disclosed compositions is the n-glycofurols.

From the foregoing, it can only be concluded that there is absolutely nothing in Bechgaard *et al.* that would motivate one of ordinary skill in the art to make the major changes to the disclosed compositions necessary to achieve Applicants' compositions. These include: removing the n-glycofurols, which is the only ingredient stated as conferring the advantageous properties to the disclosed compositions; adding about 10% water, totally contra to the disclosure of a substantially anhydrous composition that, by the inventors' own admissions, would be expected to be adversely affected by water; picking and choosing the remaining components from among the long generalized lists provided; and then combining all ingredients in the proportion given by Applicants. There is simply no guidance whatsoever to make any one of these choices, particularly wherein, as here, the two major changes are clearly opposite to the teachings of the citation.

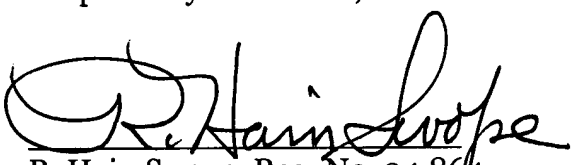
It is stated in the Office Action under reply that Bechgaard *et al.* address the same problem as Applicants. It is respectfully submitted that where, as here, compositions claims that are otherwise clearly patentable, are not rendered unpatentable because the object stated for the prior art compositions is similar.

The advantages of the compositions of the present invention for anticonvulsant therapy via transnasal administration are demonstrated by the examples in the present specification. It is shown in Example 3 that the combination of about 10% of water with a glycol and an aliphatic alcohol increases the transnasal permeation rate of diazepam approximately eight-fold over a suspension of diazepam and in Example 5 that the addition of a bile salt biological surfactant increases the rate by an further 50%. These

unexpected properties of the compositions of the present invention would in no way have been suggested to one of ordinary skill in the art from the teachings of the citation. It is therefore believed that the Examples demonstrate and support the patentability of Applicants' compositions as defined in the Claims under consideration. Withdrawal of the rejection is clearly in order and is respectfully requested.

Accordingly, it is respectfully submitted that Claims 1-8 clearly define patentable subject matter over the teachings of Bechgaard *et al.* Hence, this application is believed to be in condition for allowance. An early Notice of Allowance is courteously solicited. In the event the Examiner deems a further discussion of this application would expedite prosecution to allowance, the undersigned Attorney of Record would welcome the opportunity to hold such a discussion. The Examiner's cooperation in this regard is sincerely appreciated.

Respectfully submitted,



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